REMARKS

Amendment of the Specification

Applicants have amended description to correctly identified the chimeric that is set forth in Figure 9 as originally filed. All the tests that were performed and discussed in Example VI used the FLSC R/T IgG1 chimeric polypeptide as the testing compound.

Affirmation of Prior Election of Invention and Withdrawal of Claims 36-54 and 56-57 and Cancellation of claims 17-35 in Response to Restriction Requirement

Applicants hereby withdraw claims 36-54 and 56-57 and cancel claims 17-35 in response to the imposed restriction requirement.

Correspondingly, applicants intend to rejoin the withdrawn method claims 36-54 and 56-57 when the product claims (as herein amended, and as may subsequently be further amended) are determined to be allowable. Consistent with such intent to rejoin, applicants have amended pending method claims, notwithstanding the Office's withdrawal of such claims, to present them in form suitable for future examination upon their rejoinder with the allowed elected claims.

Rejections of Claims and Traversal Thereof

In the November 13, 2003 Office Action,

claims 1, 8 and 11 were rejected under 35 U.S.C. §102(e) as being unpatentable over Young, et al. (U.S. Patent No. 6,060,316);

claims 1, 5-16 were rejected under 35 U.S.C. §103(a) as being unpatentable over Young, et al. (U.S. Patent No. 6,060,316, hereinafter Young) and DeVico, et al (U.S. Patent No. 5,843,454, hereinafter DeVico '454) or DeVico, et al. (U.S. Patent No. 5,518,723, hereinafter DeVico '723) in view of Stratagene Catalog (1997/1998);

claims 1, 5-11 and 15-16 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3 of DeVico '723 in view of Young; and

claims 1, 5-11 and 15-16 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of DeVico '454 in view of Young.

The above-defined rejections of claims 1 and 5-16 are hereby traversed, and reconsideration of the patentability of amended claims 1 and 5-16 is requested, in light of the ensuing remarks.

Rejection under 35 U.S.C. §102(e)

Claims 1, 8 and 11 were rejected under 35 U.S.C. §102(e) as being unpatentable over Young. Applicants respectfully traverse this rejection and submit that the claims, as now amended, are not anticipated by the cited reference.

Anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, arranged as in the claim. *Lindermann Maschinenfabrik GMBH v. American Hoist and Derrick Co.*, 221 U.S.P.Q. 481, 485 (Fed. Cir. 1984). The cited reference does not meet this standard.

Applicants' amended claim 1 reads as follows:

> 1. A chimeric polypeptide comprising:
>
> a HIV virus coat polypeptide sequence and a viral receptor polypeptide sequence, **wherein the HIV virus coat polypeptide sequence has a bonding affinity for the viral receptor polypeptide sequence**, wherein the HIV virus coat polypeptide sequence and the viral receptor polypeptide sequence are linked by an amino acid spacer of sufficient length to allow the HIV virus coat polypeptide sequence and the viral receptor polypeptide sequence to bind to each other, **and wherein the HIV virus coat polypeptide is gp120 comprising a mutated furin cleavage site on the C-terminus of gp120.**

The Young reference describes a method of infecting a cell with a viral vector. To activate the viral entry of the viral vector, a soluble viral receptor-ligand fusion molecule is added. The soluble viral receptor-ligand fusion molecule comprises a viral receptor moiety that binds to the envelope component of the viral vector and a ligand moiety that binds to a cell-type specific cellular receptor. An amino acid linker may be positioned between the viral receptor moiety and the ligand moiety is of sufficient length to separate the moieties in space, thereby not restricting the ability of the soluble viral receptor-ligand

fusion molecule to bind independently and maintain the proper conformation, as stated at column 10, lines 1-5 of Young.

The Young reference does not in anyway disclose, teach or suggest that the soluble viral receptor-ligand fusion molecule comprises a gp120 polypeptide having a mutated furin cleavage site on the C-terminus of the gp120 polypeptide. Further, there is no teaching or suggestion that the viral receptor moiety and the ligand moiety having a binding affinity for each other. Instead, the Young specification states that the linker has to be of sufficient length so that the viral receptor moiety and the ligand moiety can independently bind to other moieties.

Clearly, the Young reference is not anticipatory of the applicants' claimed invention. Accordingly, applicants respectfully submit that claims 1, 8 and 11, as amended, are patentably distinguishable over Young. Withdrawal of this rejection under 35 U.S.C. §102(b) is requested.

Rejection under 35 U.S.C. §103(a)

Claims 1, 5-16 were rejected under 35 U.S.C. §103(a) as being unpatentable over Young and DeVico '454 or DeVico'723 in view of Stratagene Catalog. Applicants submit that the combination of the cited references does not in any way render applicants' claimed invention *prima facie* obvious.

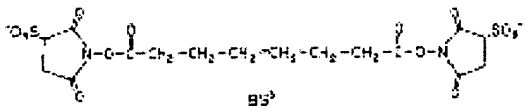
The present invention relates to a chimeric polypeptide comprising: a HIV virus coat polypeptide sequence and a viral receptor polypeptide sequence, wherein the HIV virus coat polypeptide sequence has a bonding affinity for the viral receptor polypeptide sequence, wherein the HIV virus coat polypeptide sequence and the viral receptor polypeptide sequence are linked by an amino acid spacer of sufficient length to allow the HIV virus coat polypeptide sequence and the viral receptor polypeptide sequence to bind to each other, and wherein the HIV virus coat polypeptide is gp120 comprising a mutated furin cleavage site on the C-terminus of gp120.

As discussed above, the Young reference describes a soluble viral receptor-ligand fusion molecule that comprises a viral receptor moiety that binds to the envelope component of the viral vector and a ligand moiety that binds to a cell-type specific cellular receptor. An amino acid linker may be positioned between the viral receptor moiety and the ligand moiety of sufficient length to separate the moieties in space, thereby not restricting the ability of the soluble viral receptor-ligand fusion molecule to bind independently and maintain the proper conformation, as stated at column 10, lines 1-5.

DeVico '454 and DeVico '723 disclose a gp120-CD4 covalently bonded complex that is chemically bonded together with a crosslinking agent. Thus, the virus coat polypeptide sequence and the receptor polypeptide sequence are two separate components that are **chemically cross-linked to form a receptor-ligand complex.** Both DeVico '454 and DeVico '723 expressly state that:

> "We used a covalently linked gp120-CD4 complex as an immunogen. gp120 molecules were covalently coupled to soluble recombinant CD4 using **bivalent cross-linking agents** to ensure that the integrity of the complexes was maintained during any manipulations." (emphasis added) (see column 4, lines 47-51; column 4, lines 17-21; respectively)

Furthermore, as described in the examples set forth in DeVico '454 and DeVico '723, steps were taken to permanently bond the virus coat polypeptide and viral receptor polypeptide with a bivalent cross-linking agent that covalently linked them together. Bis-sulfosuccinimidyl suberate was the crosslinking agent used in Examples I, II and III, which is a homobifunctional cross-linking reagent with amine reactivity having a structure as set forth below:



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This crosslinking agent forms a complex that is not a single chain polypeptide wherein the amino acid spacer forms peptide bonds between the terminal α-amino group of one protein and the terminal α-carboxyl group of protein. Instead the crosslinking agent binds only to primary amines on the respective proteins, and as such, the formed complex is entirely different from the chimeras of the presently claimed invention because the end product is not a polypeptide chain.

DeVico '454 and DeVico '723 expressly state that the use of the covalently bonded complex is important because prior art complexes formed through natural affinity (formed by natural attraction of receptor and ligand) did not provide for the antibodies raised strictly for the complex and instead reacted with gp 120 or CD4 (See column 2, lines 42-49; column 2, lines 41-44; respectively).

Clearly, DeVico '454 and DeVico '723 disclose only covalently bonded complexes and do not disclose, teach or suggest a chimeric polypeptide that is a linear polypeptide chain comprising a virus coat polypeptide sequence and a receptor polypeptide sequence linked by an amino acid sequence spacer

therebetween. Further neither DeVico '454 nor DeVico '723 disclose, teach or suggest in any manner that the virus coat polypeptide comprises a **mutated furin cleavage site on the C-terminus.**

According to the Office:

> "It would be obvious to one of ordinary skill in the art at the time the invention was made to utilize a chimera for the production of the gp120-CD4 complex. . . . The addition of amino acid linkers would have been obvious to the ordinary artisan in order to alleviate potential folding constraints in the fusion protein as suggested by Young, et al.(see column 10, lines 1-5)."

Applicants vigorously disagree and submit that even if all the cited references were combinable, which of course they are not, they do not describe, teach or suggest all the claim limitations recited in applicants' claimed invention.

In order to determine obviousness, it is incumbent upon the Office to view the invention as a whole. *In re Wesslau*, 174 U.S.P.Q. 393 (CCPA 1965). Also, the Office must consider the inventions of the cited references in their entireties. Certain individual features from the references may not be chosen and merely lumped together as a mosaic in an attempt to meet the features of the rejected claims. This legal concept is important for the Office to remember when attempting to combine prior art that teach entirely different structures, especially because none of the references alone or in combination discloses or recognizes the importance of **a mutated furin cleavage site on the C-terminus of the virus coat protein**.

Further, applicants submit that the Office failed to give weight to the unexpected results and advantages of the present invention as part of the "invention as a whole" and cited references that do not disclose or teach such advantages of a mutated furin cleavage site on the C-terminus of the virus coat protein.

Applicants have clearly provided in the instant specification chimeric polypeptides that exhibit unexpected and surprising results. **It is well settled that the Office must consider comparative data set forth in the specification in determining whether the claimed invention provides unexpected results**. *In re Margolis*, 228 U.S.P.Q. 940 (Fed. Cir. 1986). **Applicants' specification contains specific data indicating surprising and unexpected results.** According to the Court in *In re Soni*, 34 U.S.P.Q.2d 1684 (Fed. Cir. 1995) all evidence of nonobviousness must be considered when assessing patentability, and the PTO **must consider comparative data in the specification** in determining whether the claimed invention provides unexpected results. The basic principal behind this rule is

straightforward — that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious. The principal applies most often to the less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results.

The disclosure in the instant application underscores this point. Example VII set forth in the present application demonstrates that mutation of the furin cleavage site improves the stability of the FLSC complex. As stated at page 65 of the specification:

> "In order to determine if this putative furin site accounts for cleavage, BaLgpl20, BaLgp120 complexed with an sCD4 molecule consisting of the first two domains (VlV2) of CD4, FLSC, and FLSC R/T were captured onto plastic via an antibody specific for the C-terminus of gpl20 (antibody binding was unaffected by the R/T mutation). Four domain Vl-V4 sCD4 were titrated onto the captured complexes starting at 30 ug/ml. Four domain sCD4 has a higher affinity for gp120 than the two domain VlV2 and, therefore, would compete off the smaller unit from complexes. Bound four domain CD4 was detected with antibody OKT4, which only binds the four domain CD4. The results in FIG. 13 show that mutation of the furin cleavage site prevents the Vl V2 found on the FLSC R/T from dissociating as readily as the cleaved FLSC, thus improving its stability of the FLSC R/T complex. Introduction of the RT mutation into the BaLgp 120 c-terminus eliminates the furin mediated cleavage observed with the FLSC. Reducing this cleavage improves the continuity of the linker sequence and improves the stability of the FLSC construct (see Figure 13) by increasing the local concentration of the gp120 and CD4 moieties. The experimental result of this increase is the reduction in the ability of the soluble four domain CD4 to compete with the two domain CD4 found on the FLSC R/T."

This Example describes data demonstrating that mutation of the furin cleavage site improves the stability of the FLSC complex. The position of the cleavage site that separates the FLSC R/T fragments is located within the C terminal gp120 sequences present only in FLSC. The results show that mutation of the furin cleavage site prevents the Vl V2 found on the FLSC R/T from dissociating as readily as the cleaved FLSC, thus improving the stability of the FLSC R/T complex. As a result, the R/T mutation used to create FLSC R/T minimizes this cleavage and stabilizes the protein. Applicants reiterate that **unexpected results** obtained by mutating a furin cleavage site must be taken fully into account, pursuant to Congressional mandate for consideration of invention "as a whole."

The polypeptide structure of Young provides for the possibility of a linker positioned between the viral receptor moiety and the ligand moiety of sufficient length to separate the moieties in space, so that each of these moieties can bind to another third party target and still maintain the proper conformation of each moiety. In contrast, the DeVico '454 and '723 polypeptide structures include a virus coat polypeptide

sequence and the receptor polypeptide sequence that are **chemically cross-linked to form a receptor-ligand complex.** Thus, the Young structure has a linker that keeps the two moieties apart and the DeVico '454 and '723 structures include a crosslinking agent that binds the two moieties together into a complex. Clearly, the Young structure is entirely different from that of DeVico '454 and '723 and applicants question the combinability of such references. Applicants further assert that if the teachings of Young and DeVico '454 or DeVico '723 are combined then each individual polypeptide structures will be rendered unsatisfactory for its intended use or change the principle of operation. According to the court in *In re Gordon,* 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984), if proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, **then there is no suggestion or motivation to make the proposed modification.**

Keeping in mind that the Office is not allowed to pick and choose certain elements of Young, such as the amino acid linker, to the exclusion of other elements, applicants submit that if the amino acid linker of Young, which is meant to keep the moiety apart is incorporated into the DeVico '454 or '723 structures then the DeVico '454 or '723 will no longer function as intended. Clearly, the DeVico '454 or '723 structures were generated with the crosslinking agent for the specific reason of maintaining the integrity of complex because as stated numerous times in both DeVico '454 and '723, complexes formed by affinity binding did not provide for integrity of the complex during administration. Clearly, there is no teaching or guidance in either reference for the inclusion of a linker and more important, where the linker is supposedly positioned in the DeVico '454 and '723 structures. Is the amino acid linker added onto one end of DeVico '454 and '723 structures or does it replace the crosslinking agent. Clearly, it cannot replace the crosslinking agent because then the DeVico '454 and '723 polypeptide structures will not operate as intended if the crosslinking agent is removed.

In the reverse, if the crosslinking agent of DeVico '454 and '723 is introduced into the Young soluble viral receptor-ligand fusion molecule, the question still remains as to the placement of this crosslinking agent. If the amino acid linker is replaced by the crosslinking agent then the component moieties of the viral receptor-ligand fusion molecule may bind to each other instead of the viral receptor moiety binding to the envelope component of the viral vector and the ligand moiety binding to a cell-type specific cellular receptor. Clearly, if this replacement occurs then the Young soluble viral receptor-ligand fusion molecule will become inoperable and not provide for entry of the viral vector into the cell. In light of the fact that all reference will no longer operate as intended, there is no teaching or suggestion to go in the direction of applicants' claimed invention.

Applicants stress that the inclusion of a separation process discussed in the Stratagene Catalog does not remedy the shortcomings of the Young and DeVico '454 or DeVico '723 references.

Applicant points out that obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination and suggesting the desirability of the combination. Applicant respectfully submits that the Office's statement that "the claimed invention would be obvious to one having ordinary skill in the art" is not sufficient by itself to establish *prima facie* obviousness. According to the Board in *Ex parte Obukowicz*, 27 U.S.P.Q. 2d 1063, 1065 (B.P.A.I. 1992):

> "In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art....The examiner can satisfy this burden only by showing some **objective** (emphasis added) teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teaching of the references."

See also *Ex parte Humphreys*, 24 U.S.P.Q. 2D 1255, 1262 (B.P.A.I. 1992) where the Board addressed this very issue and determined the Office was wrong in rejecting the claims for obviousness because the examiner's rejection was not **specific** as to how one of ordinary skill in the art would have found it obvious to combine the references. Furthermore, the Board noted the examiner had not explained with any **specificity what areas of the references would suggest the combination**. This is the circumstance here. The Office has not identified **any objective or specific motivation or suggestion in the cited references that would motivate one skilled in the art to combine the references**. Thus, the Office seems to be merely reinterpreting the prior art in light of applicant's disclosure, in order to reconstruct applicant's claimed invention, but without any instructional or motivating basis in the references themselves. The Office looked at various aspects of the invention, rather than examining the invention as "a whole," found these elements separately in the art, and reassembled them to arrive at something allegedly approximating the present invention. Such approach is improper and legally insufficient to establish a *prima facie* case of obviousness.

In conclusion, the proposed combination does not render applicants' claimed invention *prima facie* obvious because there is no motivation, suggestion or basis in Young and DeVico '454 or DeVico '723 to combine the references; if the teachings of the references were combined then the respective polypeptide structures would no longer function as intended and would be rendered inoperable, and all the recited features of applicants' claimed invention are not in any way disclosed or suggested in the

cited references. Accordingly, applicants respectfully request that the rejection of claims 1 and 5-16, on the basis of obviousness, be withdrawn.

Judicially Created Doctrine of Obviousness-type Double Patenting

Claims 1, 5-11 and 15-16 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3 of DeVico '723 in view of Young or claim 1 of DeVico '454 in view of Young.

The initial burden of establishing a *prima facie* basis to deny patentability to a claimed invention is always upon the examiner. *In re Oetiker*, 977 F.2d 1443,24 USPQ 1443, (Fed. Cir. 1992). The test for obviousness-type double patenting is whether the claimed invention of the subject application would have been obvious from the subject matter of the **claims** in DeVico '454 or DeVico '723 in view of Young. *See In re Longi*, 774 F.2d 1100, 225 USPQ 645 (Fed.Cir. 1985). It should be understood that the Office is not at liberty to resort to the text of the different specifications for additional facts to support the obviousness-type double patenting. In all instances, only the literal statement of claims 1 and 3 of 'DeVico '723 or claim 1 of DeVico '454 **in view of the claims of Young** may be considered in arriving at the conclusion of obviousness.

As discussed above, applicants' claimed invention is a chimeric polypeptide comprising: a HIV virus coat polypeptide sequence and a viral receptor polypeptide sequence, wherein the HIV virus coat polypeptide sequence has a bonding affinity for the viral receptor polypeptide sequence, wherein the HIV virus coat polypeptide sequence and the viral receptor polypeptide sequence are linked by an amino acid spacer of sufficient length to allow the HIV virus coat polypeptide sequence and the viral receptor polypeptide sequence to bind to each other. Furthermore, the HIV virus coat polypeptide (gp120) comprises a mutated furin cleavage site on the C-terminus of gp120.

The DeVico '454 and '723 claims describe a virus coat polypeptide sequence and the receptor polypeptide sequence that are covalently bonded to each other. The claims of these references provide no teaching or suggestion to include an amino acid linker between the virus coat polypeptide sequence and the receptor polypeptide sequence. Further the claims of these references provide no teaching or suggestion that the virus coat polypeptide sequence is mutated at a C-terminus furin cleavage.

The claims of the Young reference provide **no** suggestion or teaching for an amino acid linker and they are completely devoid of any mention of a virus coat polypeptide sequence that is mutated at a C-terminus furin cleavage site. Thus, one reading the claims of DeVico '454 or DeVico '723 in view of the claims of Young would not be motivated to go in the direction of applicants' claimed invention.

Clearly, the question to be asked in whether there is a patentable distinction between the claims of DeVico '454 or DeVico '723 in view of the claims of Young and applicants' claimed invention. Applicants' inclusion of a mutation at a C-terminus furin cleavage site of gp120 is patentably distinct from any reference that teaches a gp120 sequence that does not include this mutation. The complexes claimed in DeVico '454 or DeVico '723 in view of the soluble molecules claimed by Young that are completely devoid of this mutated furin cleavage site do not rendered applicants' claimed invention as obvious. Because the Office has not provided the applicants with any factual basis and/or rationale to support the conclusion that the claimed invention is an obvious variation of DeVico '454 or DeVico '723 in view of Young, the judicially created double patenting rejection cannot stand. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Fees Payable

Applicants have added 2 new independent claims, and as such, $86.00 is due for entry of this amendment. The total fee of $86.00 is authorized to be charged in the attached credit card authorization form. In the event any fee or charge is properly payable in connection with the entry of this Amendment the United States Patent and Trademark Office is hereby authorized to charge the amount to Deposit Account No. 08-3284 of Intellectual Property/Technology Law.

CONCLUSION

Applicants have satisfied the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Winkler reconsider the patentability of claims 1-16, in light of the distinguishing remarks herein and withdraw all rejections, thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the event that any issues remain, Examiner Winkler is requested to contact the undersigned attorney at (919) 419-9350 to resolve same.

Respectfully submitted,

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